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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/564,792	06/05/2006	Daniel Henry Densham	GJE-1058	3347

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EXAMINER	
WILDER, CYNTHIA B	
ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/564,792	DENSHAM, DANIEL HENRY	
	Examiner	Art Unit	
	CYNTHIA B. WILDER	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 September 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15 and 20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15 and 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment filed 9/16/2008 is acknowledged and has been entered. Claim 1 has been amended. Claims 16-19 have been canceled. Claim 20 has been added. Claims 1-15 and 20 are pending. All of the arguments have been thoroughly reviewed and considered but are not found persuasive for the reasons discussed below. Any rejection not reiterated in this action has been withdrawn as being obviated by the amendment of the claims.

This action is made FINAL.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Previous Rejection

3. The prior art rejections under 35 USC 103(a) are maintained and discussed below.

Claim Rejections - 35 USC § 103

4. Once again, claims 1-9, 11, 14 and 15 rejected under 35 U.S.C. 103(a) as being unpatentable over by Nilsson et al {Nilsson I, herein) (Journal of Molecular recognition, vol. 10, page 7-17, 1997) in Nilsson et al {Nilsson II, herein} (WO 9609407, citation made or record in IDS filed 5/11/2007).

Regarding claim 1, Nilsson I teach a method for monitoring the amplification of a plurality of different target polynucleotides comprising carry out a reaction for the amplification of a plurality of different target polynucleotides, during the amplification reaction, contacting different amplified products with a molecule that binds to or interact

with a polynucleotide, the molecule being located in a spatially defined position and detecting the interaction between the amplified products and the molecules by measuring changes in applied radiation (page 8-9).

Nilsson I does not teach wherein the amplification and detection process in carried out in a single reaction chamber.

Nilsson II teaches a similar to that of Nilsson I for monitoring the amplification of a target polynucleotide in a single reaction chamber, the method comprising carrying out a reaction for the amplification of a target polynucleotide, during the amplification reaction contacting the amplified product with a molecule that binds to or interact with a polynucleotide, the molecule being located in a spatially defined position or being determined by a non-linear or non-fluorescent technique and detecting the amplified product and the molecule by measuring changes in applied radiation (see pages 4, lines 23-26, page 6, lines 10-37 and pages 9-12). Nilsson II teaches that this process is advantageous because it allows the possibilities of monitoring the actual progress of activities for quantifying a nucleic acid molecule (see pages 1-2).

On of ordinary skill in the art at the time of the claimed invention would have been motivated to have modified the nucleic acid quantification method of Nilsson I to encompass a single reaction chamber rather than multiple reaction vessels for the advantages of monitoring the actual progress of activities which takes place during the quantification of the nucleic acid as taught by Nilsson II. The instant claims are prima facie obvious over the teachings of Nilsson I and Nilsson II in the absence of secondary consideration.

Regarding claim 2, Nilsson I teaches wherein the molecule is immobilized to a support material (page 8-9).

Regarding claim 3, Nilsson II teaches wherein the method can be modified to encompass different reagents to enhance the signal during detection. These reagents include DNA polymerase enzyme, antibodies, or free nucleotides (page 12, lines 30-38).

Regarding claim 4, Nilsson I teaches wherein the molecule is a polynucleotide, at least a portion of which is complementary to a region on an amplified product (pages 8-9).

Regarding claim 5 and 6, Nilsson I teaches wherein the oligonucleotide or short nucleic acid sequences capable of use as a primer in amplification reaction or a probe in hybridization (see page 8 and 10).

Regarding claim 9, Nilsson I teaches wherein the detecting is carried out by measuring changes in Surface Plasmon Resonance (SPR) (page 8-9).

With regards to the claims 7-9, 11, and 14, these claims merely recite a plethora of conventional nucleic acid manipulation reagents and methodologies, as well as well as routine optimization or reaction components, concentrations, and parameters. Clearly such conventional and trivial modification and optimizations do not contribute towards patentability. For example, Nilsson et al teach a plurality of biosensor technologies which are known and used in the art (see entire reference, especially page 4, line 26-37 to page 5, lines 1-37). Thus, one of ordinary skill in the art would have been motivated to modify the primary references in the manner of the claims to achieve the expected benefits, optimizations and/or expanded applications. It would have been

prima facie obvious to one of ordinary skill in the art at the time of the invention to carry out the claimed methods using any of the plethora of non-linear or non-fluorescent techniques associated with biosensor technologies known in the art.

Regarding claim 15, Nilsson II teaches wherein flow cells are used in the reaction. The references do not expressly teach that the reaction vessels are sealed. However, as noted in MPEP 2144.07, it is *prima facie* obvious to select a known process based on its suitability for the intended purpose. In this case, Nilsson I teaches the use of flow cells for performing the hybridization reaction and Nilsson II teaches the use of flow based sensor chips for carrying the coamplification and hybridization reaction. Given the teachings in both Nilsson I and Nilsson II, it would have been obvious to one of ordinary skill in the art to encompass flow cells that are sealed for maintaining and monitoring the reaction conditions. The claim is *prima facie* obvious in the absence of secondary consideration.

5. Claims 10, 12 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nilsson I in view of Nilsson II and further in view of Sun et al (20040161750, filing date 2/14/2003). Regarding claims 10, 12, and 13, Nilsson I and Nilsson II teach a method for monitoring an amplification reaction as previously discussed above. The references do not expressly teach wherein the molecule comprises a metallic particle or wherein the detection is carried out using an intercalating label that binds to form a hybrid or wherein the intercalating label is fluorescent.

Su et al provide a method similar to that of Nilsson I and Nilsson II for monitoring an amplification reaction, the method comprises carrying out a reaction for the

amplification of a target polynucleotide in combination with detection via a non-linear or non-fluorescent technique (0034-0056). Su et al teach wherein the fluorescent tags are conjugated to the oligonucleotide probes (0034-0037). Su further teaches wherein in some cases nanoparticles such as gold or silver may be attached to the oligonucleotide probe array (0045, 0047). Su et al teach that the use of fluorescent label, including nanotags are advantageous for increase sensitivity and specification of detection of the target molecule (0007).

One of ordinary skill in the art at the time of the claimed invention would have been motivated to modify the nucleic acid quantification method of Nilsson I and Nilsson II to encompass fluorescent tags for the obvious benefit of increasing sensitivity and specificity of biomolecule detection as suggested by Su et al.

Response to Arguments

6. Applicant traverses the rejection on the following grounds: Applicant states that states that the combination of the cited references do not teach or suggest the claimed invention. Applicant states that the Nilsson et al and Nilsson et al references teach that nucleic acid amplification products of PCR amplification are detected only after the amplification reaction is complete. Applicant states that in contrast, in the claimed invention wherein the monitoring of the amplification progress is accomplished during the reaction(s) is both surprising and advantageous and is not taught or suggested by the cited references. Applicant states that the Nilsson 1997 reference teaches away from the claimed invention and that of the Nilsson et al (WIPO document). Applicant states that even if the references were combinable, the ordinary artisan would not arrive

at the claimed invention. Applicant states that the Nilsson et al reference describes a method of detecting amplified nucleic acids after the amplification reaction is complete. Applicant states that the technique disclosed by the Nilssion et al reference involve an initial PCR amplification followed by a physically separate detection step and further provide ssDNA for use in the subsequent detection step. Applicant states that the Examiner has not provided reasoning for her assertion that the use of a single reaction chamber for both amplification and monitoring steps would be obvious to one of ordinary skill in the art. Applicant concludes that the Examiner has provided hindsignt reconstruction of the prior art. Applicant further asserts that the references teaches that the amplification and detection steps must be carried out separately. Applicant states that further the references do not disclose a multiplex amplification reaction that is monitored during the reaction nor is there a teaching in the Nilsson et al references of a single apparatus for performing and monitoring a polynucleotide amplification reaction during amplification. Applicant states that with the citation of the Su et al reference, it does not cure the deficiencies of the Nilsson et al (1997) and Nilsson et al (WIPO document) references. Applicant requests withdrawal of the rejections under 35 USC 103.

7. All of the arguments have been thoroughly reviewed and considered but are not found persuasive for the reasons that follow: In response to applicant's arguments of surprising and unexpected results, MPEP states that "objective evidence which must be factually supported by an appropriate affidavit or declaration to be of probative value includes evidence of unexpected results, commercial success, solution of long-felt

need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant. See, for example, *In re De Blauwe*, 736 F.2d 699, 705, 222 USPQ 191, 196 (Fed. Cir. 1984). In this case, Applicant has not provide any evidence of any unexpected or surprising results. This argument is not found persuasive. In regards to Applicant's arguments concerning the order of the methods steps as taught by Nilsson I and Nilsson II, MPEP 2144.04 notes "selection of any order of performing process steps is *prima facie* obvious in the absence of new or unexpected results". Further, it is noted that the claims as currently written do not recited wherein the "detection of the amplified product occurs during the amplification reaction, but rather the claims recited wherein the "amplified products are contacted with a molecule that binds to or interacts with a polynucleotide during the amplification reaction". MPEP states "although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims". See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Nonetheless contrary to Applicant's arguments, Nilsson et al II provides this limitation. Nilsson II teaches wherein the detection of the interaction of the molecule which interacts with the amplified product may be carried out during a PCR reaction in the same reaction chamber (see pages 4-5, 6, 9-12).

In response to Applicant's arguments that the teachings of Nilsson I teaches away from the instant invention and from the teachings of Nilsson II, it is noted that Applicant does not provide any evidence to support this conclusion. Further, the Examiner disagrees because both Nilsson I and Nilsson II are directed to subject

matters that are similar in scope. The only difference is that Nillson II provides sufficient motivation for the ordinary artisan to predictably perform the method steps of Nilsson I in the same reaction chamber with a reasonable expectation of success. Applicant's attention is directed to *KSR Int'l Co. v. Teleflex Inc.* (550 U.S.____, 127 S. Ct. 1727 (2007)) where the Supreme Court determined that "a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103 (*KSR*, 550 U.S. at ____, 82 USPQ2d at 1397)." The Supreme Court also determined that "[t]he combination of familiar elements according to known methods is likely to be obvious when the combination does no more than yield predictable results (KSR, 550 U.S. at ___, 82 USPQ2d at 1395)."

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). In this case both Nilsson I and Nilsson II are drawn to methods for monitoring amplification of a target polynucleotide(s). The only difference between the references is that Nilsson I teach monitoring the amplification of a plurality of different target

polynucleotides and Nillsson II teaches monitoring a single target polynhyucleotide within a single in a single reaction chamber. Nilsson II further provides motivation for wanting to perform a method of monitoring amplification of a target polynucleotide in the same reaction chamber. Thus, the examiner maintains that the combination of Nilsson I and II is not improper hindsight reconstruction of the prior art, but rather sufficient evidence of *a prima facie* case of obviousness. The combination of Nilsson I and Nilsson II and further in view of Su et al in maintained on the same grounds discussed above. Applicant's arguments are not sufficient to overcome the prior art rejection. Accordingly, the rejections under 35 USC 103(a) are maintained.

New Ground(s) of Rejections

THE NEW GROUND(S) OF REJECTIONS WERE NECESSITATED BY APPLICANT'S AMENDMENT OF THE CLAIMS:

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claim 20 is rejected under 35 U.S.C. 103(a) as being unpatentable over Nilsson I and Nilsson II teach a method for monitoring an amplification reaction as previously discussed above. Nilsson et al teach further teach a plurality of biosensor technologies which are known and used in the art, wherein the biosensor technologies comprises non-fluorescent and non-linear techniques (see entire reference, especially page 4, line 26-37 to page 5, lines 1-37). Such modifications are considered routine optimization of known techniques or routinely used techniques. Routine optimization is not considered inventive and no evidence has been presented that the selection of method for determining the location of the molecule was other than routine, or that the technique(s) used should be considered unexpected in any way as compared to the closest prior art. Thus, one of ordinary skill in the art at the time of the claimed invention would have been motivated to modify the primary references in the manner of the claims to achieve the expected benefits, optimizations and/or expanded applications. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to carry out the claimed methods using any of the plethora of known non-linear or known non-fluorescent techniques associated with biosensor technologies as suggested by Nilsson II with a reasonable expectation of success.

Conclusion

11. No claims are allowed. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CYNTHIA B. WILDER whose telephone number is (571)272-0791. The examiner can normally be reached on a flexible schedule.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

12/11/2008

/GARY BENZION/
Supervisory Patent Examiner, Art Unit 1637